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Supporting Information

The Dutch Resolution Variant of Classical Resolution of Racemates by Formation of Diastereomeric Salts: Family Behaviour in Nucleation Inhibition

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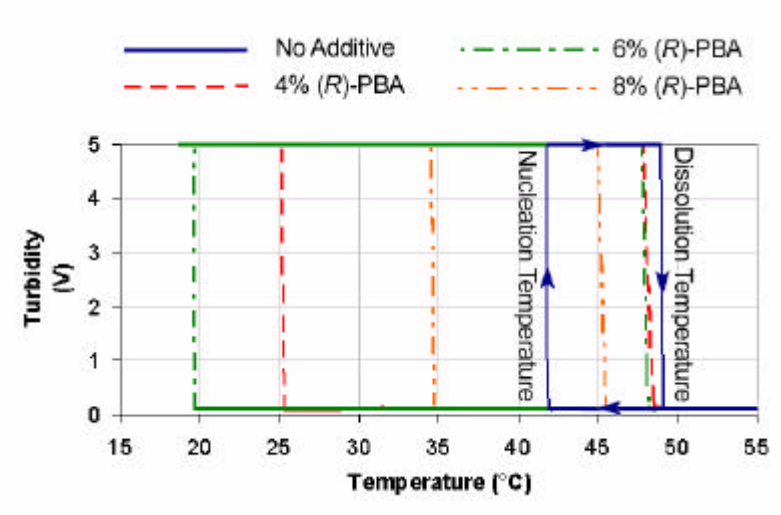
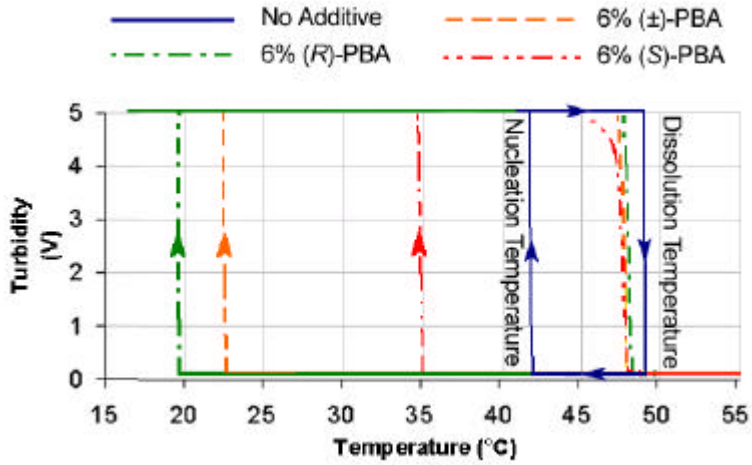
Figure S1 and Table S1. Nucleation and dissolution temperatures of the more soluble diastereomeric salt (*S*)-**1**/(*R*)-**2a**[i] at different concentrations of (*R*)-PBA (additive (*R*)-**2c**) in order to determine the optimum concentration.



Entry	Amount of Additive	Nucleation Temp. (°C)	Dissolution Temp. (°C)	Width Metastable Zone (°C)
1	–	41.8	49.1	7.3
2	4 %	25.2	48.5	23.3
3	6 %	19.7	48.2	28.5
4	8 %	34.6	45.6	11.0

[i] Concentration of the more soluble diastereomeric salt used in the turbidity measurements is 1.58 mmol·mL^{-1} in $CH_3CH(OH)CH_3$.

Figure S2 and Table S2. Turbidity measurements on the more soluble diastereomeric salt (*S*)-**1**/(*R*)-**2a**[i] in the absence and presence of 6 mol % of (*R*)-, (±)- or (*S*)-**2c**.

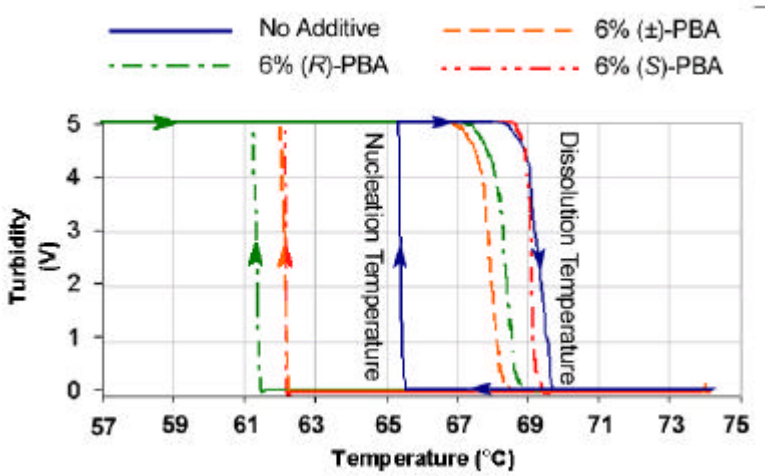


Entry	Additive	Nucleation Temp. (°C)	Dissolution Temp. (°C)	Metastable Zone Width (°C)
1	–	41.8	49.1	7.3
2	6% (*R*)-**2c**	19.7	48.2	28.5
3	6 % (±)-**2c**	22.5	47.8	25.3
4	6% (*S*)-**2c**	34.8	47.8	13.0

[i] Concentration of the more soluble diastereomeric salt used in the turbidity measurements is 1.58 mmol·mL^{-1} in $CH_3CH(OH)CH_3$.

The decision to use 6 mol% inhibitor for first screening, was based on the observation (Table S1) that this led to the greatest width of the metastable zone.

Figure S3 and Table S3. Turbidity measurements on the less soluble diastereomeric salt (*R*)-**1**/(*R*)-**2a**[i] in the absence and presence of 6 mol % of (*R*)-, (±)- or (*S*)-**2c**.



Entry	Additive	Nucleation Temp. (°C)	Dissolution Temp. (°C)	Metastable Zone Width (°C)
1	–	65.4	69.3	3.9
2	6% (*R*)-**2c**	61.4	68.4	7.0
3	6 % (±)-**2c**	62.1	68.0	5.9
4	6% (*S*)-**2c**	62.1	69.2	7.1

[i] Concentration of the less soluble diastereomeric salt used in the turbidity measurements is 0.12 mmol·mL^{-1} in $CH_3CH(OH)CH_3$.

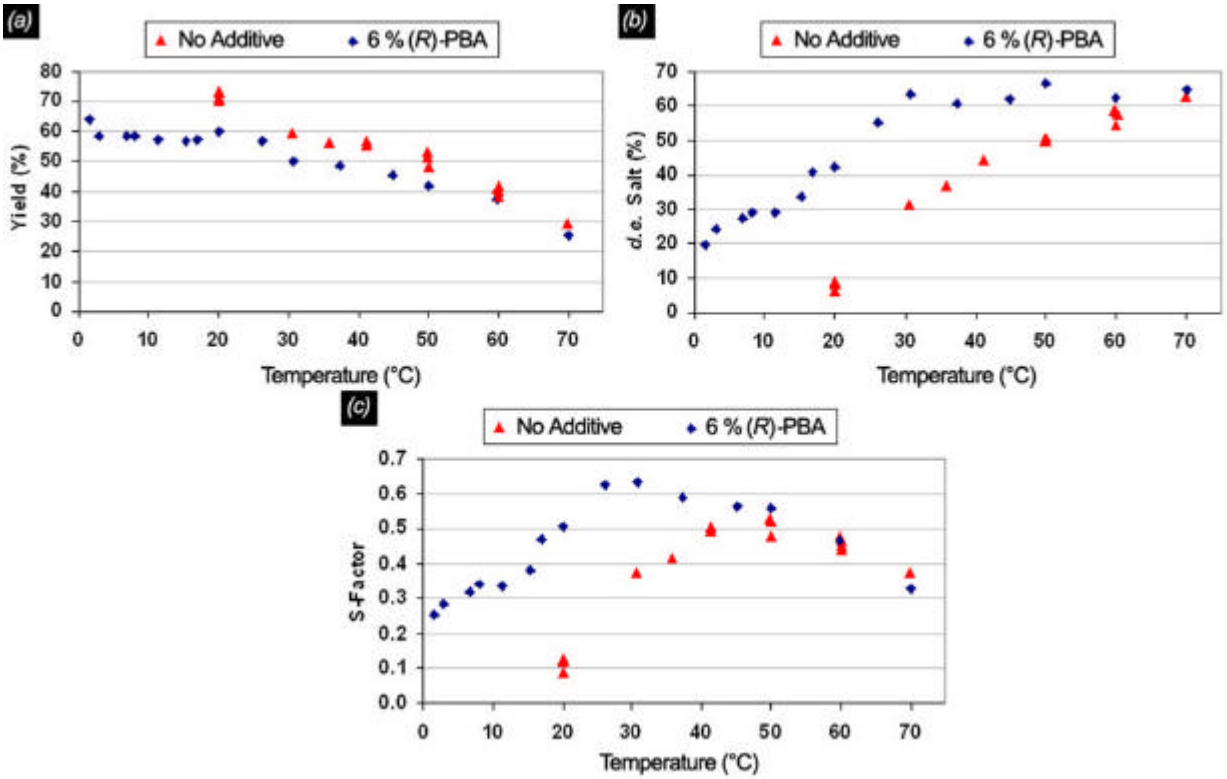
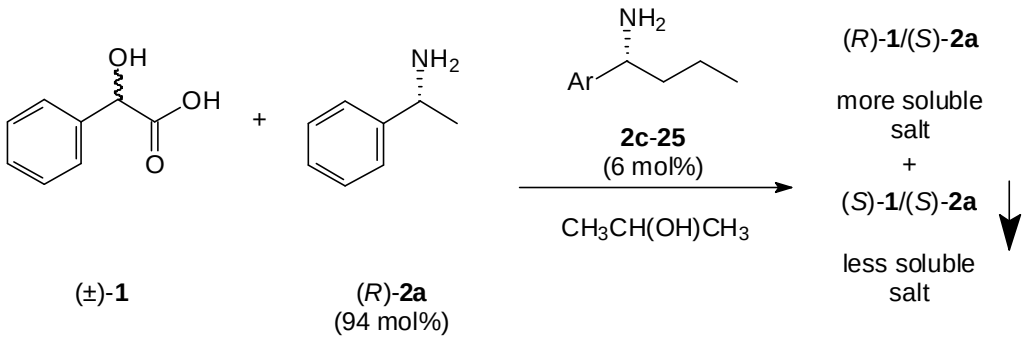


Figure S4a–c. Crystallization behaviour as a function of temperature in the absence and presence of (*R*)-**2c**. Concentrations as described in general procedure for the small scale resolutions.

Table S4 Screening for potential nucleation inhibitors in the second generation Dutch Resolution of (±)-**1** in the presence of 6 mol % of 1-arylbutylamines **2c**–**25** as additive.



(±)-**1** (*R*)-**2a** (94 mol%)

Entry	Additive		Yield (%)[a]	*de* (%)[b]	S Factor[d]
	Ar	1-Arylbutylamine			
1	No additive	–	68	14	0.19
2	C_6H_5	**2c**	60	42	0.50
3	*o*-Me C_6H_4	**19**	64	27	0.35
4	*m*-Me C_6H_4	**14**	63	24	0.30
5	*p*-Me C_6H_4	**13**	66	22	0.29
6	*o*-OMe C_6H_4	**21**	62	29	0.36
7	*m*-Ome C_6H_4	**15**	59	25	0.30
8	*p*-OMe C_6H_4	**16**	74	21	0.31
9	*o*-F C_6H_4	**22**	62	30	0.37
10	*m*-F C_6H_4	**6**	63	23	0.29
11	*p*-F C_6H_4	**18**	65	25	0.33
12	*o*-Cl C_6H_4	**7**	67	18	0.24
13	*m*-Cl C_6H_4	**3**	66	1	0.01
14	*p*-Cl C_6H_4	**17**	60	27	0.32
15	*o*-Br C_6H_4	**4**	65	8	0.10
16	*m*-Br C_6H_4	**4**	64	8	0.10
17	*p*-Br C_6H_4	**11**	62	20	0.27
18	*o*-Ph C_6H_4	**10**	64	16	0.20
19	*m*-Ph C_6H_4	**8**	57	9	0.10

20	*p*-Ph C_6H_4	**9**	67	15	0.20
21	*o:p*-NO_2 C_6H_4	**12**	63	23	0.29
22	*m*-NO_2 C_6H_4	**25**	59	44	0.52
23	*o*-OH C_6H_4	**23**	67	31	0.42
24	1-naphthyl	**24**	58	38	0.44
25	2-naphthyl	**20**	64	27	0.35

Concentration = 0.40 mmol·mL^{-1} $CH_3CH(OH)CH_3$. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts. [c] S = 2 × yield × *de*.

Table S5. Screening for potential nucleation inhibitors in the second generation Dutch Resolution of (±)-**1** in the presence of 6 mol% of additives **26**-**41**.

Entry	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1	No additive	–	68	14	0.19
2	**26**	6	62	16	0.20
3	(±)-**27**	6	63	17	0.21
4	**28**	6	67	18	0.24
5	(±)-**29**	6	64	19	0.24
6	(*R*)-**30**	6	59	39	0.46
7	(±)-**31**	6	62	22	0.27
8	**32**	6	62	22	0.28
9	(±)-**33**	6	60	24	0.29
10[a]	(*R*)-**34**		66	25	0.33
10[b]	(±)-**34**	6	66	22	0.29
10[c]	(*S*)-**34**		67	17	0.23
11[a]	(*R*)-**35**		59	34	0.40
11[b]	(±)-**35**	6	63	29	0.37
11[c]	(*S*)-**35**		67	20	0.27
12	**36**	6	65	23	0.30
13	(±)-**37**	6	65	29	0.38
14	(**±**)-**38**	6	66	30	0.40
15[a]	(*R*)-**39**		62	34	0.42
15[b]	(±)-**39**	6	64	32	0.41
15[c]	(*S*)-**39**		62	31	0.38
16[a]	(*R*)-**40**		57	26	0.29
16[b]	(±)-**40**	6	57	23	0.26
16[c]	(*S*)-**40**		61	16	0.20
17	(±)-**41**	6	57	40	0.46

Concentration = 0.40 mmol·mL^{-1} $CH_3CH(OH)CH_3$. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts. [c] S = 2 × yield × *de*.

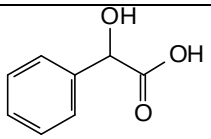
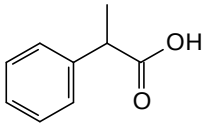
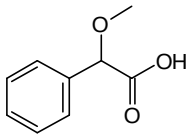
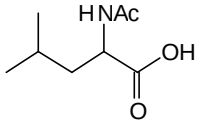
Table S6. Screening for potential nucleation inhibitors in the second generation Dutch Resolution of (±)-**1** in the presence of bifunctional amine additives **42**–**45**.

Entry	Additive	Additive (%)	Yield (%)[a]	*de* (%)[b]	S Factor[c]
1[a]	(**±**)-**42**	3	50	58	0.58
1[b]	(±)-**42**	6	51	42	0.43
2[a]	(±)-**43**	3	64	44	0.56
2[b]	(±)-**43**	6	50	45	0.45
3[a]	(*R*,*R*)-**44**	3	54	48	0.52
3[b]	(*R*,*R*)-**44**	6	51	46	0.47
4[a]	(*R*,*R*)-**45**	3	63	44	0.56
4[b]	(*R*,*R*)-**45**	6	61	67	0.82

Concentration = 0.40 mmol·mL^{-1} $CH_3CH(OH)CH_3$. [a] Isolated yield of the first salts. [b] *de* of the first isolated salts. [c] S = 2 × yield × *de*.

Table S7. Fast and direct HPLC analysis of the resolution experiments.

We developed the possibility to perform a direct analysis of the first isolated salts in Dutch Resolution experiments with **1**, **46** and **47** by tuning the conditions of the HPLC-analysis. All possible components in the salt (parent resolving agent **2c**, the additive (if present !) and both enantiomers of the substrate) have well defined and well separated retention times. This requirement was thoroughly tested for all additives independently on forehand. In resolution experiments with **48**, the substrate was liberated from the salt (by acid-base extraction) for HPLC analysis.

Entry	Substrate	HPLC column	Conditions	Ret. Times (min.)
1[a]	 (±)-**1**	Chiralpak AD (250×4,6 mm)	hexane:*i*-propanol:TFA (90:10:0.1) 1.0 mL·min^{-1}	26.5 (*R*) 30.5 (*S*)
2[a]	 (±)-**46**	Chiralcel OB (250×4,6 mm)	heptane:ethanol:TFA (99:1:0.2) 1.0 mL·min^{-1}	40.2 (*S*) 56.5 (*R*)
3[a]	 (±)-**47**	Chiralcel AS-RH (250×4,6 mm)	25 mM KH_2PO_4 buffer (*p*H=2): Acetonitrile (92:8) 0.3 mL·min^{-1}	35.7 (*S*) 38.9 (*R*)
4	 (±)-**48**	Chirobiotic T (250×4,6 mm)	methanol:acetic acid:TEA (99.5:0.1:0.1) 1.0 mL·min^{-1}	4.4 (*S*) 18.4 (*R*)

[a] For preparation of the sample for HPLC-analysis simply 0.5 mg of the salt was dissolved in 10 mL *i*-propanol.